85-2- Rat - Dermal Absorption

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DATA EVALUATION REPORT

Study Type: Deraml Absorption in Rats

Tox. Chem. No.: 2980

Accession No.: 407321-05

EPA File Symbol:

Test Material: Simulated Metolachlor 7.8 EC Formulated Product Containing ^{14}C-CGA-154281 (2.8% of the total formulation)

Synonyms/CAS No.:

Study Number(s): ABR-87086

11/15/88

Sponsor: Ciba-Geigy Corporation, Greensboro, NC

Testing Facility: Ciba-Geigy Corp. Biochemical Department

Title of Report: Dermal Absorption of CGA-154281 in Rats

Author(s): T. Murphy and B. Simoneaux

Report Issued: December 17, 1987

Conclusions:

^{14}C-CGA-154281 was rapidly absorbed in rats over a 2, 4, 10, or 24 hour exposure period. The total amount absorbed (excreta, blood, carcass and washed skin) in treated animals was from 27.5% to 55.7% of the applied dosage levels (10 or 1 mg/rat) after a 24-hour exposure period. The rate of absorption of ^{14}C-CGA-154281 was inversely related to the dosage level. Thirteen to fourteen percent of radioactivity was found in the dissolved skin after washing at both dosage levels. Eleven to thirty-four percent of the dose was excreted in a 24-hour period.

Classification of Data: Supplementary
(Deficiency: reporting of dermal absorption data)

PC 91508

Title of Study: Dermal Absorption of CGA-154281 in Rats
Ciba-Geigy Corp. Study No. ABR-87086, December 17, 1987

I. Objective: The objective of this study was to obtain information pertaining to skin absorption and excretion rates of ^{14}C-CGA-154281 when administered dermally to rats as a single dose. Data was also obtained to estimate the relative percentage of the applied dose that could be removed from the treated area.

II. Test Material and Method:

1. Test Material

CGA-154281 labeled with ^{14}C in the ring had a specific activity of 24.4 uCi/mg. Radioactive purity as determined by TLC analysis was 98%. The dermal absorption study was conducted utilizing a simulated metolachlor 7.8 EC formulation containing ^{14}C-CGA-154281 (2.8%) on male rats over a 2, 4, 10 or 24 hour exposure period at two targeted dosage levels (1 and 10 mg/rat).

2. Animal

Sprague-Dawley albino rats (50-54 days old; 200-300 grams) from Charles River Breeding Laboratories, Madison, Wisconsin, were used for this study (16 male rats per dose group). Animals considered suitable for the study were housed for a minimum 14-day acclimation period. The test animals were housed individually in Nalgene type metabolism units after dosing with radioactive test material under a controlled environmental conditions. The basal ration, Purina Certified Rodent Chow #5002, and tap water were provided ad libitum to all animals.

3. Test Material Administration

A single dermal dose of labeled test material was administered to each test animal. On the day prior to test material administration, the anterior dorsal hair was shaved from each rat with a small animal clipper. The dosing area was 10 sq. cm (4.0 by 2.5 cm) located on the upper back portion of the rat. The appropriate amount of ^{14}C-CGA-154281 suspension (50 ul for the low dose animals and 100 ul for the high dose animals) was applied to the test site using a positive displacement glass pipet. After dosing, the treated area was allowed to air dry and the entire treated area was enclosed by a nonocclusive covering consisting of Whatman No. 1 filter paper and an aluminum bridge. The aluminum foil bridge, which was slightly curved to elevate the filter paper, was glued to each side of the Stomahesive in order to cross directly over the center of the dose area.

4. Data Collection

At the time of sacrifice the animal was anesthetized by CO_2 inhalation. The entire Stomahesive appliance was removed by hand pressure and each component (Stomahesive, aluminum bridge, and paper) was separated and placed into individual glass jars with 50 ml of methanol. The treated skin area was then washed with a detergent solution, folowed by a wash with deionized water also. After washing, two samples of skin were removed; the dosed area (skin I) and the surrounding skin covered by the appliance (skin II). The skin samples were placed into 50 ml of BTS-450 Solubilizer (Beckman) and digested at 50°C overnight (16 hours) in a Lab-Line Orbit Environ-shaker. The dissolved skins were brought to a 100 ml total volume with toluene. Urine and feces were collected at the time of sacrifice and a cage wash was done using a 50:50 methanol/water solution. The following samples were analyzed at the time of sacrifice: skin I, skin II, soap rinse, water rinse, paper rinse, Stomahesive rinse, bridge rinse, urine, feces, cage wash, paper, gauze squares, blood, and carcass.

5. Radioassay Procedures and Calculation

The scintillation cocktail used for directly aliquoted samples was Scint-A (Packard Instrument Corp.). Combusted samples were assayed and counted in Oxosol-^{14}C (National Diagnostics). Combustion efficiencies were determined using a ^{14}C-benzoic acid standard. All counting was carried out by a Beckman Model LS-3801 liquid scintillation counter and efficiencies determined by external standardization.

Calculation and reduction of data obtained from this study was done using a desk top A600 model computer network (Hewlett-Packard) and an Apple IIC data package. The statistical data was based on radioactive counting.

III. Reported Results:

1. Test Material Analysis: Before dosing and after dosing on each test material application day, duplicate portions of radioactive test material preparations were diluted and analyzed in triplicate for ^{14}C.

Results: The mean counts of ^{14}C in each test material preparation were 0.7 uCi/50 ul for the low dose group and 6.59 uCi/100 ul for the high dose group (Table 1 attached). Dose variability for the two dosage levels was summarized in Table I (attached). Standard deviations were $\pm$0.005% and $\pm$0.004%for the low and high dosage levels, respectively.

2. Body Weights: Body weights of each animal were recorded prior to randomization, dosing and sacrifice.

   Results: Body weights of male rats treated with 1 mg/rat and 10 mg/rat were normal for rats of this age and strain (Table 3 attached).

3. 2-Hour Exposure: As shown in Tables II and III, a total of 39.77% of the applied low dose (1 mg/rat) and 17.3% of the applied high dose (10 mg/rat) were absorbed in excreta, blood, carcass and washed skin of test animals after 2-hour exposure period of the topically application. The total amount absorbed in washed skin (dosed area and the surrounding skin covered by the appliance) was 27.59% and 15.72% for the low and high dosage levels, respectively. One percent of the applied doses (1 or 10 mg/rat) was eliminated in urinary excreta.

4. 4-Hour Exposure: Following the topically applications of benefin on test animals for 4 hours, a total of 28.23% of the applied low dose and 23.73% of the applied high dose were absorbed in excreta, blood, cacass and washed skin (Tables II and III). The total amount absorbed in washed skin (dosed area and the surrounding skin covered by the appliance) was 21.6% and 21.04% for the low and high dosage levels, respectively. One percent of the applied doses (1 or 10 mg/rat) was eliminated in urinary excreta.

5. 10-Hour Exposure: The study authors reported that "... The rate of absorption of ^{14}C-CGA-154281 is inversely related to the doasge level. After a 10-hour period, the total amount absorbed (excreta, blood, carcass, and washed skin) was 49.4% and 25.4% for the low and high dosage levels, respectively (Figures 2 and 3 attached). Five percent to seventeen percent of the dose was excreted in 10-hour period (figures 4 and 5 attached). The main route of excretion was via the urine. After 10 hours, 47.5% of the applied low dose and 72.7% of the applied high dose could be removed from the skin by detergent wash (Figures 6 and 7 attached). "

6. 24-Hour Exposure: The study authors reported that "... Total ^{14}C recover mean values were 98.8% for the low dose level and 97.9% for the high dose level (Tables II and III attached). After a 24-hour exposure period, the total amount absorbed (excreta, blood, carcass, and washed skin) was 55.7% and 27.5% for the low and high dose levels, respectively (Figures 2 and 3 attached). The rat of absorption of ^{14}C-CGA-154281 is inversely related to the dosage level. Eleven to thirty-three percent of the dose was excreted in a 24 hour period. The main route of excretion was via the urine (Figures 4 and 5). After 24 hours, 35.5% of the applied low dose and 66.4% of the applied high dose were removed by a detergent wash (Figures 6 and 7). The amount of dose remaining in the skin was 14.2% and 13.2% for the low and high dosage levels, respectively. Thirteen to fourteen percent of the radioactivity considered to be absorbed was found in the di-dissolved skin after washing at both dosage levels. "

IV. Reported Conclusion:

The study authors concluded that " After a 10-hour exposure period, the total amount absorbed (excreta, blood, carcass, washed skin) was 49.4% and 25.4% for the low and high dosage levels, respectively. After a 24-hour exposure period, the total amount absorbed (excreta, blood, carcass, washed skin) was 55.7% for the low dose level and 27.5% for the high dose level. The extra 14-hour exposure period between 10 and 24 hours did not significantly increase the amount of absorption of CGA-154281. The rate of absorption of ^{14}C-CGA-154281 is inversely related to the dosage level. For all dosage levels, 5% to 33% was excreted in either a 10 or 24 hour period. The main route of excretion was via the urine. ..."

V. Assessment of Study Results:

1. Test Material Analysis: The radioassay results of biochemical analysis indicated that the dose variability for the two applied dosage levels of ^{14}C-CGA-154281 were found within normal range (i.e., Standard Deviation: ± 0.005% for 1 mg/rat; ± 0.004% for 10 mg/rat). From the stability studies of each dose samples showed that ^{14}C-CGA-154281 dose suspensions were stable under the experimental condition of skin.

2. Excetion Data: For both dosage levels, excretion of administered radioactivity was progressively increased from two to twenty-four hours (from 1% to 33%). We conclude, in agreement with the authors, that the main route of excretion was via the urine.

3. Although the study design was adequate and complete, the conduct and reporting of dermal absorption areas were deficient.

   As the authors noted, the total amount of ^{14}C-CGA-154281 absorbed in test animals for the 2, 4, 10, and 24 hour time points was shown to be progressively increased from two to twenty-four hours at the high dosage level (i.e., 2 hrs, 17.3%; 4 hrs, 23.7%; 10 hrs, 25.4%; 24 hrs, 27.51%), but, no dicernible time-related pattern was demonstrated at the low dosage level in this study (i.e., 2 hrs, 39.8%; 4 hrs, 28.2%; 10 hrs, 49.4%; 24 hrs. 55.7%). The reporting errors in calculation of the percent of dose in carcass and the total amount (%) absorbed in animals treated with ^{14}C-CGA-154281 for the low dose level (1 mg/rat) group after 2-hour exposure period must be corrected and recalculated in order to meet the acceptability level (i.e, The experimental error, 38.31% of the applied low dose recovered in the carcass of Animal No. R4985 after 2-hour exposure period - Appendix Table I, must be discrded for all the calculations in this study report).

4. Therefore, the report is unacceptable in the present form. However the study may be upgraded on resolution of the reporting deficiency.

Classification of Data: Supplementary

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